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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/121,798	07/23/98	BRIDENBAUGH	R 018484-00120

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 09/121,798	Applicant(s) Bridenbaugh et al
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Sep 23, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The use of the trademarks FRACTOGEL, ULTIPOR, SARTORPURE, MIRACLOTH, CENTRASETTE, VANTAGE A, CENTRAMATE and MILLIPAK have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being vague and indefinite in step "f)". The step calls for neutralizing the "precipitate mixture", but the "precipitate

mixture" has been centrifuged in the previous step "e)", therefore, the "precipitate mixture" has been converted into a "clarified solution" and a "pellet". The step is unclear as to how to neutralize the "precipitate mixture" after it has been precipitated and centrifuged.

5. Claim 18 recites the limitation "the supernatant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 17-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,011,148. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only substantial differences between the claimed invention and that disclosed by US Pat. No.

6,011,148 is the use of static mixers in the plasmid isolation prior to the use of ultrafiltration and or anion exchange chromatography in a plasmid procedure that can be readily automated.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maniatis, Marquet et al. (of record), US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 (of record).

The claims are drawn to a method of purifying plasmid DNA from bacterial cells by lysing the cells, flowing the lysis mixture through a static mixer, adding a precipitating solution, flowing the lysis mixture through a static mixer, centrifuging the precipitation mixture producing a pellet and a clarified solution comprising the plasmid DNA, neutralizing the clarified solution, passing the clarified solution over a ion exchange resin and eluting the isolated plasmid DNA. There may be a step of adding RNase digestion. The lysis solution may contain alkali. The precipitation solution may contain potassium acetate. The neutralization step may precede the centrifugation step. The steps may be combined and the procedure may be automated.

Maniatis taught (see pages 86, 87, 90 and 91) a general method for plasmid purification from bacterial cells which comprised lysing the cells, adding a precipitating solution, centrifuging the precipitation mixture producing a pellet and a clarified solution comprising the plasmid DNA, neutralizing the clarified solution. The lysis solution may contain alkali. The precipitation solution may contain potassium acetate.

Maniatis did not teach flowing the lysis mixture through a static mixer, passing the clarified solution over a ion exchange resin and eluting the isolated plasmid DNA, a step of adding RNase digestion nor that the steps may be combined and the procedure may be automated.

Marquet et al. (see especially page 46, column 2 and figures 1 and 3), US Pat No. 4,621,061 (see especially columns 3 and 4) and US Pat No. 4,830,969 (see especially columns 3 and 4) taught modifications of the general method of Maniatis which included a neutralization of the precipitation mixture prior to centrifugation, a RNase treatment step, an anion exchange step, and automation of the method.

US Pat No. 5, 837,529 taught (see the entire patent) the advantageous use of static mixers in the lysis and precipitation steps of an automated method of production of large volumes of plasmid DNA.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the basic plasmid purification method of Maniatis with the modifications of the method of Maniatis as set forth in Marquet et al., US Pat No. 4,621,061, US

Pat No. 4,830,969 and US Pat No. 5,837,529 to produce the instant claimed invention because, as stated, the methods of Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 were modifications of the general teachings of Maniatis, and each of the elements were well known to those of skill in the art to be practiced and combined as suited the situation.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the basic plasmid purification method of Maniatis with the modifications of the method of Maniatis as set forth in Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 to produce the instant claimed invention because Marquet et al. taught a general scheme for large scale plasmid purification which included all of the steps of the instant claimed invention except for the use of static mixers and the RNase treatment, US Pat No. 4,621,061 taught a scheme for large scale purification which included the steps of the method except the use of static mixers and RNase digestion, US Pat No. 4,830,969 taught a scheme for large scale purification which included the steps of the method except the use of static mixers, and US Pat No. 5,837,529 taught the use of static mixers in the lysis and precipitation steps where they state at column 3 "[a] key advantage of the present invention is that multi-liter amounts of solution containing multi-gram amounts of cells can be lysed rapidly, making large scale biological procedures involving cell lysis feasible". All of these methods were modifications of the general teachings of Maniatis, and each of the elements were well known to those of skill in the art to be practiced and combined as suited the situation. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the

producing the instant claimed invention given the teachings of Maniatis with Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529.

10. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maniatis with Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 and further in view of US Pat No. 5,300,433 in view of US Pat No. 5,034,324, US Pat No. 5,256,294, US Pat No. 5,707,812, Hubble et al. and Rembhotkar et al.

The claims are drawn to a method as described above, and to a method further comprising ultrafiltering the supernatant solution where a (polarization) gel layer is formed by the ultrafiltration process. The molecular weight cutoff of the ultrafiltration membrane may be from about 50K to about 500K daltons. The filtration device may be an open channel device.

Maniatis with Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 taught the method as described above.

Maniatis with Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 did not teach a method further comprising ultrafiltering the supernatant solution where a (polarization) gel layer is formed by the ultrafiltration process. The molecular weight cutoff of the ultrafiltration membrane may be from about 50K to about 500K daltons. The filtration device may be an open channel device.

US Pat No. 5,300,433 taught (see especially columns 15 and 16 and the claims) the process of using a polarization gel layer to fractionate and concentrate a pharmaceutical

comprising a protein by ultrafiltration using a pressure of 5 psi in a stirred cell with membranes which had a molecular weight cutoff of about 100-300 K daltons.

US Pat No. 5,034,324 taught (see especially the abstract and columns 2-4, 7-16 and the claims) the process of using a polarization gel layer to fractionate and concentrate double stranded DNA from single stranded DNA by ultrafiltration using a pressure of 5-20 atmospheres with membranes which had a molecular weight cutoff of about 100-1000 K daltons.

US Pat No. 5,256,294 taught (see especially the abstract and columns 4-12) the process of using a polarization gel layer to fractionate and concentrate a composition comprising a small molecular weight component by tangential flow filtration (with and without screens) ultrafiltration using a pressure of 5-10 psi with membranes which had a molecular weight cutoff of about 1-1000 K daltons.

Hubble et al. taught (see especially the summary and introduction) the use of a (polarization) gel layer to produce an ultrafiltration membrane. Hubble et al. discuss the theoretical and practical use of (polarization) gel layers to predictably and practically perform ultrafiltration concentration and fractionation methods.

Rembhotkar et al. taught (see the entire article) the fractionation and concentration of DNA by tangential flow ultrafiltration where a (polarization) gel layer formed to effect the separation and concentration of the DNA.

US Pat No. 5,707,812 taught (see especially columns 6-7) the obvious combination of ultrafiltration and ion exchange chromatography for purification, concentration, fractionation and desalting plasmid DNA.

It would have been obvious to one of ordinary skill in the art at the time of the instant claimed invention to combine the method to concentrate, fractionate, purify and desalt a protein using a (polarization) gel layer in an ultrafiltration device as taught by US Pat No. 5,300,433 with the methods of concentration, fractionation, purification and desalting the DNA's and plasmids of US Pat No. 5,034,324, US Pat No. 5,256,294, US Pat No. 5,707,812, Hubble et al. and Rembhotkar et al. because they all taught the advantageous use of (polarization) gel layers in ultrafiltration devices to concentrate, fractionate, purify and desalt compositions comprising DNA's.

One of ordinary skill in the art would have been motivated at the time of the instant claimed invention to combine the method to concentrate, fractionate, purify and desalt a protein using a (polarization) gel layer in an ultrafiltration device as taught by US Pat No. 5,300,433 with the methods of concentration, fractionation, purification and desalting the DNA's and plasmids of US Pat No. 5,034,324, US Pat No. 5,256,294, US Pat No. 5,707,812, Hubble et al. and Rembhotkar et al. because, US Pat No. 5,300,433 recited at column 15 lines 36-48 "although Factor IX has a molecular weight of only 60-70 K Daltons, it did not ultrafilter to a significant extent through a membrane whose porosity should have allowed its passage into the ultrafiltrate. A reasonable explanation is based on the phenomenon known as membrane polarization....The

layer may become so concentrated that it become(s) 'gelatinous' and constitutes a new form of membrane overlying that in use." US Pat No. 5,034,314 recited at column 7, lines 30-56 "a membrane filter can be used to separate single-stranded (e.g. unhybridized) from hybridized nucleic acids....Our discovery is as unexpected as finding that a spaghetti colander would pass certain forms (and retain slightly wider forms) of pasta, even though the colander's holes in both cases are much bigger than the diameter of both forms of pasta." US Pat No. 5256,294 recites at column 4, lines 33-37 "although concentration polarization can be modified, and quite high filtration rates can be achieved even from very concentrated solutions if appropriate conditions are supplied, the polarization layer can never be completely eliminated". Hubble et al. recite at the bottom of the introduction, "[t]his report describes the production of thin alginate gel films for ultrafiltration". Rembhotkar et al. and US Pat No. 5,707,812 demonstrate the obvious application of methods well known in the art to concentrate, purify, fractionate, and desalt nucleic acids using ultrafiltration. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Maniatis with Marquet et al., US Pat No. 4,621,061, US Pat No. 4,830,969 and US Pat No. 5,837,529 and US Pat No. 5,300,433 with US Pat No. 5,034,324, US Pat No. 5,256,294, US Pat No. 5,707,812, Hubble et al. and Rembhotkar et al.

Conclusion

11. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
January 3, 2000

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